

REMARKS

Telephone Interview

Applicants express appreciation to the Examiner for the courtesy extended to Applicants' representatives, inventor Dr. Philippa Marrack and Applicants' agent Dr. Angela Dallas Sebor, during the telephone interview of October 20, 2005. During the interview, the rejection under 35 U.S.C. 103 was discussed. Specifically, Applicants' representatives presented arguments against the combination of Zhang et al., Lenardo and Refaeli et al., which included the argument that Lenardo or Refaeli et al. are each directed to the effect of IL-2 on mature, activated T cells, and that neither reference teaches that one should inhibit IL-2 to enhance memory T cell stimulation. Applicants' representatives further discussed that the portion of Lenardo referenced by the Examiner was mere speculation and was non-enabling. When asked by Applicant's agent where in the references was the motivation to combine Lenardo and/or Refaeli et al. with Zhang et al., the Examiner agreed that each of the references was silent with regard to the teachings of the other. With regard to the Examiner's contention that the references directed to mature T cells (Lenardo or Refaeli et al.) would motivate one of skill in the art to produce a vaccine or adjuvant to achieve these effects, Dr. Marrack responded that vaccines or adjuvants are not designed with the goal of having an impact on mature T cells; rather, vaccines and adjuvants are designed only to affect memory T cells. The Examiner indicated that Applicants should respond to the Office Action and that the arguments would be considered.

Rejection of Claims 1-3, 9, 14-15 and 52 Under 35 U.S.C. § 103

The Examiner has rejected Claims 1-3, 9, 14-15 and 52 under 35 U.S.C. § 103, contending that these claims are unpatentable over Zhang et al. in view of Lenardo and Refaeli et al. Zhang et al. is again cited as teaching that IL-15 causes a strong and selective stimulation of memory T cells. The Examiner states that Zhang et al. differs from the claimed invention only in that it does not teach the use of IL-15 in an adjuvant formulation or the inclusion of an IL-2 antibody in the formulation. Lenardo is cited as teaching that IL-2 is required for programmed cell death of mature, antigen activated T cells and further that cells that escape IL-2-induced apoptosis may become memory T

cells. Refaeli et al. is cited for allegedly expanding on the teachings of Lenardo. Specifically, the Examiner contends that Refaeli et al. conclude that IL-2 is involved in T cell homeostasis. The Examiner contends that it would have been obvious to combine these references to arrive at the claimed invention, and that one would have been motivated to combine IL-15 and stimulate memory T cells and to remove IL-2 and reduce T cell ACID.

With regard to Applicants' prior argument that Zhang et al. teach that IL-2 has a minimal stimulatory effect on memory T cells, the Examiner asserts that since this effect is insignificant in most cases, the reference is deemed to be essentially neutral on the inhibition of IL-2 in memory T cell production. With regard to Applicants' prior argument that Lenardo teaches away from the inhibition of IL-2 and that IL-2 inhibition had no effect on T cells in the absence of antigen, the Examiner asserts that it is unclear how Applicants' argument regarding the presence or absence of antigen is relevant, since the claims do not exclude antigen. The Examiner states that the reference of Lenardo teaches that T cells that escape ACID become memory T cells. The Examiner contends that additional motivation to make the combination is provided by Refaeli et al.

Applicants traverse the rejection of Claims 1-3, 9, 14-15 and 52 under 35 U.S.C. § 103.

With regard to the contribution of Zhang et al. to the combination, Applicants maintain the prior position that one of skill in the art viewing the teachings of Zhang et al. would either do nothing with regard to IL-2 or would *provide* IL-2 to try to achieve at least the minimal added stimulation of memory phenotype observed by Zhang et al. The Examiner responds to this argument by stating that he considers Zhang et al. to be essentially neutral on the topic of IL-2. The Examiner repeated this point in the interview by stating that the each of the references are silent with regard to the teachings of the other. Therefore, at a minimum, Applicants and the Examiner agree that Zhang et al. provides no motivation to inhibit IL-2 or to make the combination with Lenardo and Refaeli et al. Applicants additionally maintain that there is a *teaching away* from inhibiting IL-2 in Zhang et al. for the reasons of record. Therefore, the only motivation to combine the references as the Examiner has done should be found in Lenardo and/or in Refaeli et al. Applicants submit that there is no motivation or expectation of success found in these references that would lead one of skill in the art to make the combination with Zhang et al. as the Examiner has done, or to make and use

the presently claimed invention. Applicants further note that the Examiner has acknowledged in the October 20 interview that each of the cited references is silent with regard to the teachings of the other, which would seem to be an agreement that the direct motivation to combine the references is lacking in the combination. Applicants believe that there is no motivation of any kind to make the combination, which is discussed below.

With regard to Lenardo and Refaeli et al., as discussed with the Examiner during the October 20 interview, while the Examiner asserts that Lenardo teaches "that T cells that escape AICD become memory T cells", Applicants' position is that the only sentence in Lenardo that mentions memory T cells at all is purely speculation and is not actually a *teaching* of any effect on memory T cells by Lenardo. First, as previously argued, Lenardo does not know or evaluate the effect of IL-2 on memory T cells at all, but merely *suggests* that some responding T cells *might* escape death and become memory cells. Lenardo provides no evidence that this statement is correct and does not investigate T cells of a memory phenotype at all. Therefore, Applicants submit that Lenardo is completely non-enabling with regard to any effect of IL-2 on memory T cells and as such, there is no expectation of success that inhibition of IL-2 would have an impact on memory T cells. Second, even *if* one considers the speculative statement by Lenardo, as discussed in the October 20 interview, it is Applicants' position that there would again be no motivation to inhibit IL-2 to enhance memory T cells. Specifically, if such cells are already *refractory* to the effects of IL-2, as one would have to infer from Lenardo's speculative statement, then there would be no reason to inhibit IL-2 to enhance memory T cells. Lenardo does not speculate that T cells that otherwise undergo apoptosis in the presence of IL-2 may go on to become memory T cells if IL-2 is inhibited; this is rather the Examiner's apparent extrapolation of the statement in Lenardo.

The Examiner cites Refaeli et al. as expanding on the teachings of Lenardo and providing further motivation to make the present invention, but Applicants submit that like Lenardo, Refaeli et al. is only directed to the investigation of the effects of IL-2 on mature, activated T cells. Refaeli et al. do not evaluate memory T cells or provide any teachings regarding memory T cells and in fact, Applicants are unable to find any statement in Refaeli et al. relevant to memory T cells. Therefore, it is unclear how this reference provides any further teachings or motivation with regard to the

claimed invention. The Examiner relies on the position that one would be motivated to provide an agent that inhibits IL-2 in a vaccine or adjuvant because it protects mature activated T cells from AICD. However, as Dr. Marrack discussed with the Examiner in the October 20 interview, the goal of producing a vaccine or adjuvant is not to affect mature activated T cell responses, such as AICD. Rather, they are designed to enhance memory T cell responses. In any event, there is no evidence provided by Lenardo or Refaeli et al. that protection of mature activated T cells from AICD will enhance memory T cells. Moreover, as discussed above, Zhang et al. did not find any significant effect of IL-2 on memory T cells, and the minimal observed effect was stimulation of memory T cells. Therefore, from either point of view (Zhang et al. or Lenardo/Refaeli et al.), the combination of references does not support the Examiner's contention that there is a motivation to arrive at the present invention.

Furthermore, Applicants enclose herewith a Declaration under 37 CFR 1.132 by Yosef Refaeli, who is the first author of the cited Refaeli et al. Dr. Refaeli states that his opinion is that one can not assume based on the teachings of Lenardo or his own publication that T cells that are affected by AICD are related to memory cells and that there are no data provided in Lenardo or his own publication to support such a hypothesis. Dr. Refaeli further states that he has reviewed the present claims and does not appear to him based on the citations of record to be obvious that inhibition of IL-2 will stimulate memory T cells.

The Examiner also states that it is unclear how the issue of antigen is relevant to Applicants' argument. Applicants submit that the issue is relevant because it reveals differences between mature, activated T cells as studied in Lenardo and Refaeli et al., versus T cells of a memory phenotype. Applicants have argued that one can not extrapolate the teachings of Lenardo and Refaeli et al. to predict an effect on memory T cells, and the necessity for antigen in Lenardo illustrates this point. First, because Lenardo is evaluating mature T cells, he must use antigen in conjunction with the IL-2 to observe any effect. As discussed previously, Lenardo teach that in the absence of antigen stimulation, inhibition of IL-2 has *no effect* on the stimulation of T cells (see prior response). Therefore, even *if* one tried to extrapolate the teachings of Lenardo to speculate about some effect on memory T cells, one would not inhibit IL-2 without also providing concurrent antigen

stimulation. The claims do not exclude the presence of antigen, but the claims also do not require antigen. This is because antigen is optional; it is not required by the claimed composition to achieve the desired affect on memory T cells. Perhaps more importantly, however, is the point that the requirement for antigen in Lenardo emphasizes a difference between mature T cells and memory T cells that is relevant to the issue of motivation to arrive at the present invention. As described in the art (see Background of the present specification), memory T cells and T cells with memory phenotype continue to divide, albeit slowly, in the absence of antigen (*i.e.*, they undergo slow division). Therefore, memory T cells can be stimulated in the absence of antigen, in contrast to mature T cells. The lack of an effect on T cells by anti-IL-2 in Lenardo in the absence of antigen illustrates that the T cells that Lenardo investigating are not memory T cells, behave differently than memory T cells, and therefore, that effects on such cells may not be extrapolated to memory T cells. In contrast, the present inventors have demonstrated that memory T cells are in fact stimulated by anti-IL-2 in the *absence* of antigen, which is directly in contrast to the teachings of Lenardo (see Example 3 of the present specification). Therefore, Applicants submit that any conclusions drawn by Lenardo with regard to mature T cells can not simply be applied to predict an effect on memory T cells.

Finally, the present invention provides surprising and unexpected results. Specifically, it was completely surprising to the inventors that the memory T cells display such a profound response to the regulation of IL-2, since, as discussed by Dr. Marrack in the October 20 interview, memory T cells express very little CD25 (IL-2 α). Prior to the present invention, there was no teaching or suggestion that inhibition of IL-2 would have a direct effect on memory T cell survival and division.

In summary, Applicants again submit that the Examiner has failed to provide the requisite motivation to combine the references and that the combination of references fails to provide a reasonable expectation of success at making and using the presently claimed invention.

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In view of the foregoing remarks, the Examiner is respectfully requested to withdraw the rejection of the claims under 35 U.S.C. § 103.

Respectfully submitted,

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